

What is claimed is:

1. A sustained-release oral dosage form comprising a subunit, wherein the subunit comprises an opioid analgesic and a sustained-release material, wherein the dissolution rate *in-vitro* of the subunit, when measured by standard USP Drug Release test of U.S. Pharmacopeia (2003) <724>, is:
  - a. less than about 10% within about 6 hours and at least about 60% within about 24 hours;
  - b. less than about 10% within about 8 hours and at least about 60% within about 24 hours;
  - c. less than about 10% within about 10 hours and at least about 60% within about 24 hours; or
  - d. less than about 10% within about 12 hours and at least about 60% within about 24 hours;the dosage form providing a duration of therapeutic effect of about 24 hours.
2. The oral dosage form of claim 1, wherein the opioid analgesic is selected from the group consisting of morphine, oxycodone, hydrocodone, or any combination thereof.
3. The oral dosage form of claim 1, wherein the opioid analgesic is morphine.
4. The oral dosage form of any of claims 1-3, which further comprises at least one release-retarding material.
5. The oral dosage form of claim 4, wherein the release-retarding material is selected from the group consisting of acrylic polymers, cellulose, alkylcelluloses, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and combinations thereof.
6. The oral dosage form of claim 4, which further comprises a plasticizer.
7. The oral dosage form of claim 5, wherein the plasticizer is selected from the group consisting of dibutyl sebacate, diethyl phthalate, dibutyl phthalate, triethyl citrate, tributyl citrate, triacetin, castor oil, polyethylene glycols, and propylene glycol.
8. The oral dosage form of claim 4, which further comprises at least one release-modifying agent.

9. The oral dosage form of claim 6, which further comprises at least one release-modifying agent.

10. The oral dosage form of claim 8 or 9, wherein the release-modifying agent is selected from the group consisting of hydroxypropylmethylcellulose, lactose, hydroxypropylcellulose, polyvinyl pyrrolidone, sodium lauryl sulfate, metal stearates, and combinations thereof.

11. A method of treating pain comprising orally administering to a human on a once-daily basis the oral sustained-release dosage form of any of claims 1-3, whereupon pain in the human is treated.

12. The method of claim 11, wherein the oral sustained-release dosage form further comprises at least one release-retarding agent and at least one plasticizer.

13. The method of claim 12, wherein the oral sustained-release dosage form further comprises at least one release-modifying agent.

14. The method of any of claim 11, wherein the dosage form is efficacious in a human in the fed or fast state.

15. The oral dosage form of claim 1, wherein the maximum dissolution rate is from about 10% to about 25% per hour.

16. The oral dosage form of claim 1, wherein the maximum dissolution rate is from about 10% to about 50% per hour.

17. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 6 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 25% per hour.

18. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 6 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 50% per hour.

19. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 8 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 25% per hour.

20. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 8 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 50% per hour.

21. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 10 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 25% per hour.

22. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 10 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 50% per hour.

23. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 12 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 25% per hour.

24. The oral dosage form of claim 1, wherein the dissolution rate *in-vitro* of the subunit is less than about 10% within about 12 hours and at least about 60% within about 24 hours and the maximum dissolution rate is from about 10% to about 50% per hour.

25. A sustained-release oral dosage form comprising a first subunit and a second subunit, wherein the first subunit comprises a first opioid analgesic and the second subunit comprises a second opioid analgesic, wherein the first and second opioid analgesics can be the same or different, wherein the first subunit releases substantially all of the first opioid analgesic within about 12 hours and the second subunit releases less than about 10% of the second opioid analgesic within about 6 hours and at least about 60% of the second opioid analgesic within about 24 hours, wherein the dissolution rate *in-vitro* is measured by standard USP Drug Release test of U.S. Pharmacopeia XXVI (2003) <724>, such that:

- a. the oral dosage form releases from about 35% to about 65% of the first and second opioid analgesic after about 10 hours;
  - b. the oral dosage form releases not more than about 10% of the first and second opioid analgesic after about 1 hour; or
  - c. the oral dosage form releases not less than about 70% of the first and second opioid analgesic after about 20 hours,
- the dosage form providing a duration of therapeutic effect of about 24 hours.

26. The oral dosage form of claim 25, wherein the opioid analgesic is selected from the group consisting of morphine, oxycodone, hydrocodone, or any combination thereof.
27. The oral dosage form of claim 26, wherein the opioid analgesic is morphine.
28. The oral dosage form of any of claims 25-27, which further comprises at least one release-retarding material and at least one plasticizer.
29. The oral dosage form of claim 28, wherein the release-retarding material is selected from the group consisting of acrylic polymers, cellulose, alkylcelluloses, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and combinations thereof.
30. The oral dosage form of claim 28, wherein the plasticizer is selected from the group consisting of dibutyl sebacate, diethyl phthalate, dibutyl phthalate, triethyl citrate, tributyl citrate, triacetin, castor oil, polyethylene glycols, and propylene glycol.
31. The oral dosage form of claim 28, which further comprises at least one release-modifying agent.
32. The oral dosage form of claim 31, wherein the release-modifying agent is selected from the group consisting of hydroxypropylmethylcellulose, lactose, hydroxypropylcellulose, polyvinyl pyrrolidone, sodium lauryl sulfate, metal stearates, and combinations thereof.
33. A method of treating pain comprising orally administering to a human on a once-daily basis the oral sustained-release dosage form of any of claims 25-27, whereupon pain in the human is treated.
34. The method of claim 33, wherein the oral sustained-release dosage form further comprises at least one release-retarding agent and at least one plasticizer.
35. The method of claim 34, wherein the oral sustained-release dosage form further comprises at least one release-modifying agent.
36. The method of claim 33, wherein the dosage form is efficacious in a human in the fed or fast state.

37. The oral dosage form of claim 1, which, at steady-state, provides:

a. a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1;

b. a maximum opioid plasma concentration ( $C_{max}$ ), and an opioid plasma concentration at about 12 hours after administration ( $C_{12}$ ), and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the average opioid plasma concentration between  $C_{max}$  and  $C_{12}$  is substantially equal to the average opioid plasma concentration between  $C_{12}$  and  $C_{24}$ ;

c. a first maximum opioid plasma concentration ( $C_{max1}$ ) between about 0 hours and about 12 hours after administration, and a second maximum opioid plasma concentration ( $C_{max2}$ ) between about 12 hours and about 24 hours after administration;

d. a first maximum opioid plasma concentration ( $C_{max1}$ ) between about 0 hours and about 12 hours after administration, a second maximum opioid plasma concentration ( $C_{max2}$ ) between about 12 hours and about 24 hours after administration, and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the average plasma opioid concentration between about  $C_{max1}$  and about  $C_{max2}$  is substantially equal to the average opioid plasma concentration between about  $C_{max2}$  and about  $C_{24}$ ;

e. a first opioid maximum plasma concentration ( $C_{max1}$ ) and a first minimum opioid plasma concentration ( $C_{min1}$ ) between about 0 hours and about 12 hours after administration, a second maximum opioid plasma concentration ( $C_{max2}$ ), and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max1}$  to  $C_{min1}$  is less than about 2:1 or the ratio of  $C_{max2}$  to  $C_{24}$  is less than about 2:1; or

f. a first maximum opioid plasma concentration ( $C_{max1}$ ) and a first minimum opioid plasma concentration ( $C_{min1}$ ) between about 0 hours and about 12 hours after administration, a second opioid maximum plasma concentration ( $C_{max2}$ ), and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the difference between the ratio of  $C_{max1}$  to  $C_{min1}$  and the ratio of  $C_{max2}$  to  $C_{24}$  is less than about 30%.

38. The oral dosage form of claim 1, wherein the dosage form, at steady state, provides:

a. a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1; or

b. a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1.

39. The oral dosage form of claim 1, which at steady-state, provides a first Area Under the Curve ( $AUC_1$ ) between 0 and about 12 hours and a second Area Under the Curve ( $AUC_2$ ) between 12 hours and about 24 hours, wherein the difference between  $AUC_2$  and  $AUC_1$  is less than about 50%.

40. An oral dosage form comprising an opioid analgesic in sustained-release form, which, at steady-state, provides:

a. a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1;

b. a maximum opioid plasma concentration ( $C_{max}$ ), and an opioid plasma concentration at about 12 hours after administration ( $C_{12}$ ), and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the average opioid plasma concentration between  $C_{max}$  and  $C_{12}$  is substantially equal to the average opioid plasma concentration between  $C_{12}$  and  $C_{24}$ ;

c. a first maximum opioid plasma concentration ( $C_{max1}$ ) between about 0 hours and about 12 hours after administration, and a second maximum opioid plasma concentration ( $C_{max2}$ ) between about 12 hours and about 24 hours after administration;

d. a first maximum opioid plasma concentration ( $C_{max1}$ ) between about 0 hours and about 12 hours after administration, a second maximum opioid plasma concentration ( $C_{max2}$ ) between about 12 hours and about 24 hours after administration, and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the average plasma opioid concentration between about  $C_{max1}$  and about  $C_{max2}$  is substantially equal to the average opioid plasma concentration between about  $C_{max2}$  and about  $C_{24}$ ;

e. a first opioid maximum plasma concentration ( $C_{max1}$ ) and a first minimum opioid plasma concentration ( $C_{min1}$ ) between about 0 hours and about 12 hours after administration, a second maximum opioid plasma concentration ( $C_{max2}$ ), and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max1}$  to  $C_{min1}$  is less than about 2:1 or the ratio of  $C_{max2}$  to  $C_{24}$  is less than about 2:1; or

f. a first maximum opioid plasma concentration ( $C_{max1}$ ) and a first minimum opioid plasma concentration ( $C_{min1}$ ) between about 0 hours and about 12 hours after administration, a second opioid maximum plasma concentration ( $C_{max2}$ ),

and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the difference between the ratio of  $C_{max1}$  to  $C_{min1}$  and the ratio of  $C_{max2}$  to  $C_{24}$  is less than about 30%.

41. A sustained-release oral dosage form comprising a first subunit and a second subunit, wherein:

a. the first subunit and the second subunit comprise an opioid analgesic, wherein the dosage form, at steady-state, provides a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1; or

b. the first subunit and the second subunit comprise an opioid analgesic, the first subunit comprises a first release-retarding material and the second subunit comprises a second release-retarding material, wherein the first and second release-retarding material can be the same or different, and wherein the dosage form, at steady-state, provides a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1.

42. An oral dosage form comprising an opioid analgesic in sustained-release form, which at steady-state, provides a first Area Under the Curve ( $AUC_1$ ) between 0 and about 12 hours and a second Area Under the Curve ( $AUC_2$ ) between 12 hours and about 24 hours, wherein the difference between  $AUC_2$  and  $AUC_1$  is less than about 50%.

43. The oral dosage form of claim 30, wherein at steady-state, provides an *in-vivo* plasma profile of a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1.

44. The oral dosage form of claim 24, wherein at steady-state, provides a dissolution profile of a maximum opioid plasma concentration ( $C_{max}$ ) and an opioid plasma concentration at about 24 hours after administration ( $C_{24}$ ), wherein the ratio of  $C_{max}$  to  $C_{24}$  is less than about 2:1.